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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

#### Declarations under Rule 4.17:

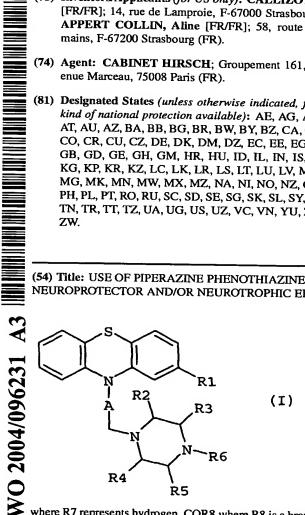
- as to the identity of the inventor (Rule 4.17(i)) for all designations
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations
- of inventorship (Rule 4.17(iv)) for US only

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- with international search report
- (88) Date of publication of the international search report: 24 March 2005

[Continued on next page]

(54) Title: USE OF PIPERAZINE PHENOTHIAZINE DERIVATIVES IN THE MANUFACTURE OF A MEDICAMENT WITH NEUROPROTECTOR AND/OR NEUROTROPHIC EFFECTS ON CNS AND/OR PNS



(57) Abstract: This invention relates to a new use of piperazinephenothiazine derivatives and their pharmaceutically acceptable salts or esters in the manufacture of a medicament with neuroprotector and/or neurotrophic effects on CNS and/or PNS. The piperazine phenothiazine derivatives are selected from compounds of formula (I) wherein A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms; R1 represents hydrogen, halogen, lower alkyl, lower alkoxy, lower alkanoyl, lower alkyl-mercapto, trifluoromethylmercapto, lower alkyl-sulfonyl (preferably methylsulfonyl), perfluoroalkyl of 1 to 3 carbon atoms; R2, R3, R4 and R5 each represent methyl, ethyl or hydrogen, R6 represents hydrogen, lower alkyl, hydroxy-lower-alkyl or aliphatic acyloxy-lower-alkyl having 1 to 4 carbon atoms in the acyloxy portion and 1 to 6 carbon atoms in the alkyl portion, CH2-CH2-O-R7

where R7 represents hydrogen, COR8 where R8 is a branched or straight chain alkyl radical of from seven to fourteen carbon atoms.

# WO 2004/096231 A3



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Intern ial Application No PCT/EP2004/005183

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/5415 A61P25/28

A61P25/16

A61P25/02

According to International Patent Classification (IPC) or to both national classification and IPC

#### **B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, WPI Data, PAJ

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X	HALE M S ET AL: "LOW DOSE PERPHENAZINE AND L DOPA CARBIDOPA THERAPY IN A PATIENT WITH PARKINSONISM AND A PSYCHOTIC ILLNESS" JOURNAL OF NERVOUS AND MENTAL DISEASE, vol. 168, no. 5, 1980, pages 312-314, XP008020514 ISSN: 0022-3018 the whole document	1-3,5,6, 10-12
X	PERINI M ET AL: "BENEFIT OF FLUOPERAZINE IN DRUG-INDUCED HALLUCINATIONS DURING PARKINSON'S DISEASE MANAGEMENT" GAZZETTA MEDICA ITALIANA ARCHIVIO PER LE SCIENZE MEDICHE, vol. 148, no. 3, 1989, pages 101-104, XP008020513 ISSN: 0393-3660 abstract	1-3,5,6, 10-12

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents:     A' document defining the general state of the art which is not considered to be of particular relevance     E' earlier document but published on or after the international filing date     L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)     O' document referring to an oral disclosure, use, exhibition or other means     Description of the international filing date but later than the priority date claimed	<ul> <li>"T" later document published after the international filing date or priority date and not in conflict with the application but clied to understand the principle or theory underlying the invention</li> <li>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</li> <li>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</li> <li>"&amp;" document member of the same patent family</li> </ul>
Date of the actual completion of the International search  29 November 2004	Date of mailing of the international search report  2 2 12. 2004
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentlaan 2  NL - 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	Authorized officer  Hornich, E

Interr<sub>i</sub> al Application No PC1/EP2004/005183

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X	WO 99/07356 A (SANBERG PAUL RONALD ;SHYTLE ROLAND DOUGLAS (US); SILVER ARCHIE AAR) 18 February 1999 (1999-02-18) abstract; claims 1,5,6,8	1-6, 10-12
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	(continuation of coronal shoot) (logues 2004)				

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Poy II. Observations where continued in the continued in
Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
Claims Nos.:     because they relate to subject matter not required to be searched by this Authority, namely:
Claims Nos.:     because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful international Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box III Observations where unity of Invention is lacking (Continuation of item 3 of first sheet)
This international Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report Covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5 (partly), 6 ,10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating Parkinson's disease

2. claims: 1-5 (partly), 7, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating Alzheimer's disease

3. claims: 1-5 (partly), 8, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating peripheral neuropathy diseases

4. claims: 1-5 (partly), 9, 10-12 (partly)

Use of piperazine phenothiazine derivatives in the manufacture of a medicament for treating amyotrophic lateral sclerosis diseases

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